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=> d his

     (FILE 'HOME' ENTERED AT 14:11:06 ON 21 OCT 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:11:28 ON 21 OCT 2003
L1       9134759 S BLOOD? OR PLASMA
L2        553896 S CLOT? OR COAGULAT?
L3        290216 S L1 AND L2
L4           950 S "PROTEIN Z"
L5         20233 S "FACTOR XA"
L6            76 S L4 AND L5
L7            99 S "PROTEIN Z INHIBITOR" OR "ZPI"
L8            56 S HUMAN AND L7
L9            40 S L8 AND L5
L10           30 S L3 AND L9
L11           13 DUP REM L10 (17 DUPLICATES REMOVED)
L12        81541 S L3 AND (PROLONG? OR INHIBIT?)
L13           35 S L7 AND L12
L14           15 DUP REM L13 (20 DUPLICATES REMOVED)
                 E BROZE G J/AU
L15          373 S E3-E5
L16           21 S L7 AND L15
L17            7 DUP REM L16 (14 DUPLICATES REMOVED)

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                  present
 NEWS  4  AUG 05  New pricing for EUROPATFULL and PCTFULL effective
                  August 1, 2003
 NEWS  5  AUG 13  Field Availability (/FA) field enhanced in BEILSTEIN
 NEWS  6  AUG 18  Data available for download as a PDF in RDISCLOSURE
 NEWS  7  AUG 18  Simultaneous left and right truncation added to PASCAL
 NEWS  8  AUG 18  FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                  Truncation
 NEWS  9  AUG 18  Simultaneous left and right truncation added to ANABSTR
 NEWS 10  SEP 22  DIPPR file reloaded
 NEWS 11  SEP 25  INPADOC: Legal Status data to be reloaded
 NEWS 12  SEP 29  DISSABS now available on STN
 NEWS 13  OCT 10  PCTFULL: Two new display fields added
 NEWS 14  OCT 21  BIOSIS file reloaded and enhanced

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               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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=> s blood? or plasma
L1     9134759 BLOOD? OR PLASMA

=> s clot? or coagulat?
L2      553896 CLOT? OR COAGULAT?

=> s l1 and l2
L3      290216 L1 AND L2

=> s inhibit? or prevent?
   7 FILES SEARCHED...
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=> s "protein Z"
L4          950 "PROTEIN Z"

=> s "factor Xa"
L5        20233 "FACTOR XA"

=> s l4 and l5
L6           76 L4 AND L5

=> s "protein Z inhibitor" or "zpi"
L7           99 "PROTEIN Z INHIBITOR" OR "ZPI"

=> s human and l7
L8           56 HUMAN AND L7

=> d his

     (FILE 'HOME' ENTERED AT 14:11:06 ON 21 OCT 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:11:28 ON 21 OCT 2003
L1      9134759 S BLOOD? OR PLASMA
L2       553896 S CLOT? OR COAGULAT?
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L3       290216 S L1 AND L2
L4          950 S "PROTEIN Z"
L5        20233 S "FACTOR XA"
L6           76 S L4 AND L5
L7           99 S "PROTEIN Z INHIBITOR" OR "ZPI"
L8           56 S HUMAN AND L7

=> s l8 and l5
L9           40 L8 AND L5

=> s l3 and l9
L10          30 L3 AND L9

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          13 DUP REM L10 (17 DUPLICATES REMOVED)

=> d 1-13 ibib ab

L11  ANSWER 1 OF 13  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER:    2002:282865  BIOSIS
DOCUMENT NUMBER:     PREV200200282865
TITLE:               Protein Z-dependent protease inhibitor.
AUTHOR(S):           Broze, George J., Jr. [Inventor, Reprint author]
CORPORATE SOURCE:    St. Louis, MO, USA
                     ASSIGNEE: Washington University
PATENT INFORMATION:  US 6369031 April 09, 2002
SOURCE:              Official Gazette of the United States Patent and Trademark
                     Office Patents, (Apr. 9, 2002) Vol. 1257, No. 2.
                     http://www.uspto.gov/web/menu/patdata.html. e-file.
                     CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE:       Patent
LANGUAGE:            English
ENTRY DATE:          Entered STN: 8 May 2002
                     Last Updated on STN: 8 May 2002
AB   The disclosure describes the purification and isolation of a novel
     human protein Z-dependent protease inhibitor (ZPI) from
     plasma characterized as having a molecular weight of about 72 kDa,
     being a single chain protein with an N-terminal amino acid sequence of
     LAPSPQSPETPA, and which produces a rapid inhibition of factor
     Xa in the presence of human protein Z (PZ), calcium ions
     and cephalin.  The disclosure further describes the isolation and cloning
     of the ZPI cDNA from a human cDNA library.  The
     ZPI cDNA is 2.44 kb in length and has an open reading frame that
     encodes the 423 residue mature ZPI protein and a 21 residue
     signal peptide.  PZ, ZPI and the combination of PZ and
     ZPI are used to inhibit blood coagulation.

L11  ANSWER 2 OF 13  EMBASE  COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:    2002210052  EMBASE
TITLE:               [Protein Z-dependent protease inhibition complex: A new
                     regulation system of blood clotting?].
                     LE COMPLEXE PROTEINE Z-INHIBITEUR DEPENDANT DE LA PROTEINE
                     Z: UN NOUVEAU SYSTEME REGULATEUR DE LA COAGULATION
                     ?.
AUTHOR:              Vasse M.
CORPORATE SOURCE:    M. Vasse, UF d'Hemostase Cellulaire, Laboratoire
                     d'Hematologie, CHRU Charles-Nicolle, 1, rue de Germont,
                     76031 Rouen Cedex, France. marc.vasse@chu-rouen.fr
SOURCE:              Sang Thrombose Vaisseaux, (2002) 14/4 (209-216).
                     Refs: 29
```

ISSN: 0999-7385 CODEN: STVAEY
COUNTRY: France
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: French
SUMMARY LANGUAGE: English; French
AB Protein Z is a vitamin K-dependent factor identified in **human plasma** in 1984 but, at that time its physiological function was poorly understood. However, it has recently been shown that protein Z is implicated in the down-regulation of **coagulation** by forming a complex with a **plasma** proteinase inhibitor called PZ-dependent protease inhibitor (**ZPI**) which inhibits activated **factor Xa** on phospholipid surfaces. In the absence of an additional challenge, the disruption of PZ gene in mice is asymptomatic, but the association with the factor V(Leiden) mutation is almost always fatal during the neonatal period with microvascular thrombosis. Unexpectedly, in **human** a relationship between protein Z deficiency and arterial (ischaemic strokes, unstable angina) but not venous thrombosis has been shown. As protein Z deficiency is frequent (5 to 10% of the general population according to the studies), yet unidentified additional factors are certainly required to explain the increased risk of arterial thrombosis. A significant amount of protein Z deficiency (20%) has also been found in early foetal loss, mainly between the 10th and the end of 19th week of gestation, when maternal and foetal circulations are connected, as well as a decrease in protein Z levels in patients with antiphospholipid syndrome. Additional larger, multicentric and prospective clinical studies are clearly required to better define the role of protein Z in **human** thromboembolic disease.

L11 ANSWER 3 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
ACCESSION NUMBER: 2002390439 EMBASE
TITLE: Protein Z influences the prothrombotic phenotype in Factor V Leiden patients.
AUTHOR: Kemkes-Matthes B.; Nees M.; Kuhnel G.; Matzdorff A.; Matthes K.J.
CORPORATE SOURCE: B. Kemkes-Matthes, Zent. Inn. Med. Justus Liebig U. G., Klinikstrasse 36, D-35385 Giessen, Germany. Bettina.Kemkes-Matthes@innere.med.uni-giessen.de
SOURCE: Thrombosis Research, (15 May 2002) 106/4-5 (183-185). Refs: 13
ISSN: 0049-3848 CODEN: THBRAA
PUBLISHER IDENT.: S 0049-3848(02)00181-0
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Protein Z enhances the inhibition of **factor Xa** by protein Z-dependent protease inhibitor (**ZPI**). Thus, diminution of protein Z should induce prothrombotic tendency due to lowered cofactor activity for **ZPI**. In Factor V Leiden mice, prothrombotic tendency of severe diminution or lack of protein Z was demonstrated. We here present first studies in **humans**, indicating that diminution of protein Z in factor V Leiden patients aggravates thromboembolic risk.

L11 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:453343 BIOSIS
DOCUMENT NUMBER: PREV200100453343
TITLE: Protein Z-dependent protease inhibitor.

AUTHOR(S): Broze, George J., Jr. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Washington University
PATENT INFORMATION: US 6271367 August 07, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 7, 2001) Vol. 1249, No. 1. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The disclosure describes the purification and isolation of a novel **human** protein Z-dependent protease inhibitor (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid inhibition of **factor Xa** in the presence of **human** protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a **human** cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to inhibit **blood coagulation**.

L11 ANSWER 5 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:435701 BIOSIS
DOCUMENT NUMBER: PREV200100435701
TITLE: Protein Z-dependent protease inhibitor.
AUTHOR(S): Broze, George J., Jr. [Inventor, Reprint author]
CORPORATE SOURCE: St. Louis, MO, USA
ASSIGNEE: Washington, University, St. Louis, MO, USA
PATENT INFORMATION: US 6265378 July 24, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 24, 2001) Vol. 1248, No. 4. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The disclosure describes the purification and isolation of a novel **human** protein Z-dependent protease inhibitor (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid inhibition of **factor Xa** in the presence of **human** protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a **human** cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to inhibit **blood coagulation**.

L11 ANSWER 6 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:340860 BIOSIS
DOCUMENT NUMBER: PREV200100340860
TITLE: Protein Z-dependent protease inhibitor.
AUTHOR(S): Broze, George J. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Washington University
PATENT INFORMATION: US 6245741 June 12, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 12, 2001) Vol. 1247, No. 2. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent

LANGUAGE: English
ENTRY DATE: Entered STN: 18 Jul 2001
Last Updated on STN: 19 Feb 2002

AB The disclosure describes the purification and isolation of a novel **human** protein Z-dependent protease inhibitor (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid inhibition of **factor Xa** in the presence of **human** protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a **human** cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to inhibit **blood coagulation**.

L11 ANSWER 7 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 2
ACCESSION NUMBER: 2001170421 EMBASE
TITLE: Mouse protein Z-dependent protease inhibitor cDNA.
AUTHOR: Zhang J.; Broze G.J. Jr.
CORPORATE SOURCE: G.J. Broze Jr., Division of Hematology, Mail Zone 90-20-662, Barnes-Jewish Hospital, 216 South Kingshighway Blvd, St. Louis, MO 63110, United States. gbroze@im.wustl.edu
SOURCE: Thrombosis and Haemostasis, (2001) 85/5 (861-865). Refs: 8
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
030 Pharmacology
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Protein Z-dependent protease inhibitor (**ZPI**) is **plasma** proteinase inhibitor in the serpin superfamily that produces rapid inhibition of **factor Xa** in the presence of phospholipids, Ca(++) and protein Z (PZ). Mouse **ZPI** cDNA was isolated and cloned from mouse liver RNA using RT-PCR. The cDNA contains 100 nucleotides 5' of a translation initiation codon and an open reading frame of 1344 nucleotides followed by a 163 nucleotide 3' untranslated sequence with a poly (A) tail. The cDNA predicts a signal peptide containing 21 amino acids and a mature protein of 427 residues with 8 potential sites for N-linked glycosylation. The oligonucleotide and predicted amino acid sequences of mouse **ZPI** are 72% and 81% homologous with those of **human ZPI**. Like **human ZPI**, mouse **ZPI** contains tyrosine-serine (P(1)-P(1)') at its reactive center in contrast to the rat molecule which contains tyrosine-cysteine. By Northern analysis, mouse **ZPI** mRNA is 1.6 kb in size and, similar to both **human** and rat, it is detectable in liver, but not in heart, brain, spleen, lung, kidney, skeletal muscle or testes.

L11 ANSWER 8 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001139693 EMBASE
TITLE: Protein Z circulates in **plasma** in a complex with protein Z-dependent protease inhibitor.
AUTHOR: Tabatabai A.; Fiehler R.; Broze G.J. Jr.

CORPORATE SOURCE: Dr. G.J. Broze Jr., Division of Hematology, Barnes-Jewish Hospital, 216 S. Kingshighway Blvd., St. Louis, MO 63110, United States. gbroze@im.wustl.edu
SOURCE: Thrombosis and Haemostasis, (2001) 85/4 (655-660).
Refs: 31
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Protein Z (PZ) is a vitamin K-dependent **plasma** protein that forms a Ca(++)-dependent complex with **factor Xa** at phospholipid surfaces. This interaction between PZ and **factor Xa** enhances by > 1000-fold the inhibition of **factor Xa** by the serpin called protein Z-dependent protease inhibitor (**ZPI**). These experiments show that PZ also binds **ZPI** in a process that does not require Ca(++) or phospholipids. In pooled normal **plasma**, which contains excess **ZPI** relative to PZ, all the PZ appears to be bound in a complex with **ZPI**. The binding of PZ to **ZPI** reduces the rate and extent of factor XIa inhibition produced by **ZPI**. During the course of these studies, it was noted that a PZ purification procedure, that included NaSCN (2.0 M) elution of PZ from an immunoaffinity column, produced aggregated, inactive forms of PZ.

L11 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001440927 MEDLINE
DOCUMENT NUMBER: 21379114 PubMed ID: 11487045
TITLE: Protein Z-dependent regulation of **coagulation**.
AUTHOR: Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, MO 63110, USA.. gbroze@im.wustl.edu
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Jul) 86 (1) 8-13. Ref: 47
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Protein Z (PZ) is a 62 kDa vitamin K-dependent **plasma** protein that serves as a cofactor for the inhibition of **factor Xa** by protein Z-dependent protease inhibitor (**ZPI**). **ZPI** is a recently identified 72 kDa member of the serpin superfamily of proteinase inhibitors that contains a tyrosine at its reactive center. PZ circulates in **plasma** in a complex with **ZPI**. Inhibition of **factor Xa** by **ZPI** in the presence of phospholipids and Ca++ is enhanced 1000-fold by PZ, but **ZPI** also inhibits factor XIa in a process that does not require PZ, phospholipids or Ca++. **ZPI** activity is consumed during **coagulation** through proteolysis mediated by **factor Xa** with PZ and factor Xla. Concomitant PZ deficiency dramatically increases the severity of the prothrombotic phenotype of factor VLeiden mice. Studies to determine the potential roles of PZ and **ZPI**

deficiency in **human** thrombosis are in progress.

L11 ANSWER 10 OF 13 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001051375 MEDLINE
DOCUMENT NUMBER: 20504046 PubMed ID: 11049983
TITLE: Characterization of the protein Z-dependent protease inhibitor.
AUTHOR: Han X; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University Medical Center, St Louis, MO 63110, USA.
SOURCE: BLOOD, (2000 Nov 1) 96 (9) 3049-55.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001211

AB Protein Z-dependent protease inhibitor (**ZPI**) is a 72-kd member of the serpin superfamily of proteinase inhibitors that produces rapid inhibition of **factor Xa** in the presence of protein Z (PZ), procoagulant phospholipids, and Ca(++) (t(1/2) less than 10 seconds). The rate of **factor Xa** inhibition by **ZPI** is reduced more than 1000-fold in the absence of PZ. The **factor Xa**-**ZPI** complex is not stable to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, but is detectable by alkaline-polyacrylamide gel electrophoresis. The combination of PZ and **ZPI** dramatically delays the initiation and reduces the ultimate rate of thrombin generation in mixtures containing prothrombin, factor V, phospholipids, and Ca(++). In similar mixtures containing factor Va, however, PZ and **ZPI** do not inhibit thrombin generation. Thus, the major effect of PZ and **ZPI** is to dampen the **coagulation** response prior to the formation of the prothrombinase complex. Besides **factor Xa**, **ZPI** also inhibits factor XIa in the absence of PZ, phospholipids, and Ca(++). Heparin (0.2 U/mL) enhances the rate (t(1/2) = 25 seconds vs 50 seconds) and the extent (99% vs 93% at 30 minutes) of factor XIa inhibition by **ZPI**. During its inhibitory interaction with **factor Xa** and factor XIa, **ZPI** is proteolytically cleaved with the release of a 4.2-kd peptide. The N-terminal amino acid sequence of this peptide (SMPPVIKVDRPF) establishes Y387 as the P(1) residue at the reactive center of **ZPI**. **ZPI** activity is consumed during the in vitro **coagulation** of **plasma** through a proteolytic process that involves the actions of **factor Xa** with PZ and factor XIa.

L11 ANSWER 11 OF 13 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2000-02957 BIOTECHDS
TITLE: New isolated **human** protein Z-dependent protease-inhibitor, used for inhibiting **Factor-Xa**, particularly for inhibiting **blood coagulation**;
recombinant **Factor-Xa**-inhibitor with anticoagulant and thrombolytic activity
AUTHOR: Broze Jr G J
PATENT ASSIGNEE: Univ.Washington
LOCATION: St. Louis, MO, USA.
PATENT INFO: WO 9960126 25 Nov 1999
APPLICATION INFO: WO 1999-US7040 13 May 1999

PRIORITY INFO: US 1998-86571 19 May 1998
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2000-062457 [05]

AB **Human** protein-Z-dependent protease-inhibiting (**ZPI**) (A) with a mol.wt. of 72,000, an N-terminal amino acid sequence of 12 residues (disclosed), and inhibits **Factor-Xa** in the presence of protein-Z, calcium ions and cephalin, is claimed. (A) is a single chain protein that gives a rapid inhibition of **Factor-Xa** in the presence of protein-Z, calcium ions and cephalin. Also claimed are: a DNA molecule comprising a sequence encoding a protein sequence of 423 amino acids (disclosed); a **ZPI** with a disclosed 423 amino acid protein sequence; a method for inhibiting **blood coagulation** involving administering protein-Z and/or **ZPI** ; and a method for inhibiting **Factor-Xa** in serum or **plasma** comprising contacting the serum or **plasma** with an inhibitor as in (A) or a protein of 423 amino acids. The **Factor-Xa**-inhibitor has anticoagulant and thrombolytic activity. The **ZPI** can be used for inhibiting **Factor-Xa** in serum or **plasma**. A DNA sequence of 2,466 bp is disclosed. (54pp)

L11 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999389569 MEDLINE
DOCUMENT NUMBER: 99389569 PubMed ID: 10460162
TITLE: The protein Z-dependent protease inhibitor is a serpin.
AUTHOR: Han X; Huang Z F; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: HL-60782 (NHLBI)
SOURCE: BIOCHEMISTRY, (1999 Aug 24) 38 (34) 11073-8. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF181467
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990923

AB In the presence of phospholipid vesicles and calcium ions, protein Z (PZ) serves as a cofactor for the inhibition of **coagulation factor Xa** by a **plasma** protein called PZ-dependent protease inhibitor (**ZPI**). To further characterize **ZPI**, its cDNA has been isolated and cloned from a **human** liver cDNA library. The **ZPI** cDNA is 2.44 kb in length and has a relatively long 5' region (466 nt) that contains six potential ATG translation start codons. ATG's 1-4 are followed by short open reading frames, whereas ATG(5) and ATG(6) are in an uninterrupted open reading frame that includes the encoded **ZPI** protein. In vitro experiments show that ATG(6) is sufficient for the expression of rZPI in cultured Chinese hamster ovary cells. Northern analysis suggests the liver is a major site of **ZPI** synthesis. The predicted 423 residue amino acid sequence of the mature **ZPI** protein is 25-35% homologous with members of the serpin superfamily of protease inhibitors and is 78% identical to the amino acid sequence predicted by a previously described cDNA isolated from rat liver, regeneration-associated serpin protein-1 (rasp-1). Thus, **ZPI** is likely the **human** homologue of rat rasp-1. Alignment of the amino acid sequence of **ZPI** with those of other serpins predicts that Y387 is the P(1)

residue at the reactive center of the **ZPI** molecule. Consistent with this notion, rZPI(Y387A), an altered form of **ZPI** in which tyrosine 387 has been changed to alanine, lacks PZ-dependent **factor Xa** inhibitory activity.

L11 ANSWER 13 OF 13 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998356143 MEDLINE
DOCUMENT NUMBER: 98356143 PubMed ID: 9689066
TITLE: Isolation of a protein Z-dependent **plasma** protease inhibitor.
AUTHOR: Han X; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, 216 South Kingshighway Boulevard, St. Louis, MO 63110, USA.
CONTRACT NUMBER: HL34462 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Aug 4) 95 (16) 9250-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980908

AB **Human** protein Z (PZ) is a 62,000-Mr, vitamin K-dependent **plasma** protein whose structure is similar to **coagulation** factors VII, IX, X, protein C, and protein S, but whose function is not known. The procoagulant activity of **factor Xa** in a one-stage **plasma coagulation** assay is reduced when **factor Xa** is first incubated with PZ. This apparent inhibitory effect is time dependent, requires the presence of calcium ions and procoagulant phospholipids (rabbit brain cephalin), and appears predominantly related to the incubation period of PZ with cephalin. In serum the initial rate of inhibition of **factor Xa** with calcium ions and cephalin also is enhanced in the presence PZ. A PZ-dependent protease inhibitor (**ZPI**) has been isolated from **plasma**. **ZPI** is a 72,000-Mr single-chain protein with an N-terminal amino acid sequence of LAPSPQSPEXXA (X = indeterminate) and an estimated concentration in citrate-treated **plasma** of 1.0-1.6 microg/ml. In systems using purified components, the **factor Xa** inhibition produced by **ZPI** is rapid (>95% within 1 min by **coagulation** assay) and requires the presence of PZ, calcium ions, and cephalin. The inhibitory process appears to involve the formation of a **factor Xa**-PZ-**ZPI** complex at the phospholipid surface.

=> d his

(FILE 'HOME' ENTERED AT 14:11:06 ON 21 OCT 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:11:28 ON 21 OCT 2003

L1 9134759 S BLOOD? OR PLASMA
L2 553896 S CLOT? OR COAGULAT?
L3 290216 S L1 AND L2
L4 950 S "PROTEIN Z"
L5 20233 S "FACTOR XA"
L6 76 S L4 AND L5
L7 99 S "PROTEIN Z INHIBITOR" OR "ZPI"

```
L8            56 S HUMAN AND L7
L9            40 S L8 AND L5
L10           30 S L3 AND L9
L11           13 DUP REM L10 (17 DUPLICATES REMOVED)

=> s l3 and (prolong? or inhibit?)
L12       81541 L3 AND (PROLONG? OR INHIBIT?)

=> s l7 and l12
L13           35 L7 AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           15 DUP REM L13 (20 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L14  ANSWER 1 OF 15  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER:   2002:282865  BIOSIS
DOCUMENT NUMBER:    PREV200200282865
TITLE:              Protein Z-dependent protease inhibitor.
AUTHOR(S):          Broze, George J., Jr. [Inventor, Reprint author]
CORPORATE SOURCE:   St. Louis, MO, USA
                    ASSIGNEE: Washington University
PATENT INFORMATION: US 6369031 April 09, 2002
SOURCE:             Official Gazette of the United States Patent and Trademark
                    Office Patents, (Apr. 9, 2002) Vol. 1257, No. 2.
                    http://www.uspto.gov/web/menu/patdata.html. e-file.
                    CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE:      Patent
LANGUAGE:           English
ENTRY DATE:         Entered STN: 8 May 2002
                    Last Updated on STN: 8 May 2002
AB   The disclosure describes the purification and isolation of a novel human
     protein Z-dependent protease inhibitor (ZPI) from
     plasma characterized as having a molecular weight of about 72 kDa,
     being a single chain protein with an N-terminal amino acid sequence of
     LAPSPQSPETPA, and which produces a rapid inhibition of factor Xa
     in the presence of human protein Z (PZ), calcium ions and cephalin.  The
     disclosure further describes the isolation and cloning of the ZPI
     cDNA from a human cDNA library.  The ZPI cDNA is 2.44 kb in
     length and has an open reading frame that encodes the 423 residue mature
     ZPI protein and a 21 residue signal peptide.  PZ, ZPI
     and the combination of PZ and ZPI are used to inhibit
     blood coagulation.

L14  ANSWER 2 OF 15  EMBASE  COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:   2002210052  EMBASE
TITLE:              [Protein Z-dependent protease inhibition complex:
                    A new regulation system of blood clotting
                    ?].
                    LE COMPLEXE PROTEINE Z-INHIBITEUR DEPENDANT DE LA
                    PROTEINE Z: UN NOUVEAU SYSTEME REGULATEUR DE LA
                    COAGULATION?.
AUTHOR:             Vasse M.
CORPORATE SOURCE:   M. Vasse, UF d'Hemostase Cellulaire, Laboratoire
                    d'Hematologie, CHRU Charles-Nicolle, 1, rue de Germont,
                    76031 Rouen Cedex, France. marc.vasse@chu-rouen.fr
SOURCE:             Sang Thrombose Vaisseaux, (2002) 14/4 (209-216).
                    Refs: 29
                    ISSN: 0999-7385  CODEN: STVAEY
```

COUNTRY: France
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: French
SUMMARY LANGUAGE: English; French
AB Protein Z is a vitamin K-dependent factor identified in human **plasma** in 1984 but, at that time its physiological function was poorly understood. However, it has recently been shown that protein Z is implicated in the down-regulation of **coagulation** by forming a complex with a **plasma** proteinase **inhibitor** called PZ-dependent protease **inhibitor** (**ZPI**) which **inhibits** activated factor Xa on phospholipid surfaces. In the absence of an additional challenge, the disruption of PZ gene in mice is asymptomatic, but the association with the factor V(Leiden) mutation is almost always fatal during the neonatal period with microvascular thrombosis. Unexpectedly, in human a relationship between protein Z deficiency and arterial (ischaemic strokes, unstable angina) but not venous thrombosis has been shown. As protein Z deficiency is frequent (5 to 10% of the general population according to the studies), yet unidentified additional factors are certainly required to explain the increased risk of arterial thrombosis. A significant amount of protein Z deficiency (20%) has also been found in early foetal loss, mainly between the 10th and the end of 19th week of gestation, when maternal and foetal circulations are connected, as well as a decrease in protein Z levels in patients with antiphospholipid syndrome. Additional larger, multicentric and prospective clinical studies are clearly required to better define the role of protein Z in human thromboembolic disease.

L14 ANSWER 3 OF 15 EMBASE
on STN DUPLICATE 1
ACCESSION NUMBER: 2002390439 EMBASE
TITLE: Protein Z influences the prothrombotic phenotype in Factor V Leiden patients.
AUTHOR: Kemkes-Matthes B.; Nees M.; Kuhnel G.; Matzdorff A.; Matthes K.J.
CORPORATE SOURCE: B. Kemkes-Matthes, Zent. Inn. Med. Justus Liebig U. G., Klinikstrasse 36, D-35385 Giessen, Germany. Bettina.Kemkes-Matthes@innere.med.uni-giessen.de
SOURCE: Thrombosis Research, (15 May 2002) 106/4-5 (183-185). Refs: 13
ISSN: 0049-3848 CODEN: THBRAA
PUBLISHER IDENT.: S 0049-3848(02)00181-0
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Protein Z enhances the **inhibition** of factor Xa by protein Z-dependent protease **inhibitor** (**ZPI**). Thus, diminution of protein Z should induce prothrombotic tendency due to lowered cofactor activity for **ZPI**. In Factor V Leiden mice, prothrombotic tendency of severe diminution or lack of protein Z was demonstrated. We here present first studies in humans, indicating that diminution of protein Z in factor V Leiden patients aggravates thromboembolic risk.

L14 ANSWER 4 OF 15 BIOSIS
ACCESSION NUMBER: 2001:453343 BIOSIS
DOCUMENT NUMBER: PREV200100453343
TITLE: Protein Z-dependent protease **inhibitor**.
AUTHOR(S): Broze, George J., Jr. [Inventor]

CORPORATE SOURCE: ASSIGNEE: Washington University
PATENT INFORMATION: US 6271367 August 07, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 7, 2001) Vol. 1249, No. 1. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The disclosure describes the purification and isolation of a novel human protein Z-dependent protease **inhibitor** (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid **inhibition** of factor Xa in the presence of human protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a human cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to **inhibit blood coagulation**.

L14 ANSWER 5 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:435701 BIOSIS
DOCUMENT NUMBER: PREV200100435701
TITLE: Protein Z-dependent protease **inhibitor**.
AUTHOR(S): Broze, George J., Jr. [Inventor, Reprint author]
CORPORATE SOURCE: St. Louis, MO, USA
ASSIGNEE: Washington, University, St. Louis, MO, USA
PATENT INFORMATION: US 6265378 July 24, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 24, 2001) Vol. 1248, No. 4. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The disclosure describes the purification and isolation of a novel human protein Z-dependent protease **inhibitor** (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid **inhibition** of factor Xa in the presence of human protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a human cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to **inhibit blood coagulation**.

L14 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:340860 BIOSIS
DOCUMENT NUMBER: PREV200100340860
TITLE: Protein Z-dependent protease **inhibitor**.
AUTHOR(S): Broze, George J. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Washington University
PATENT INFORMATION: US 6245741 June 12, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 12, 2001) Vol. 1247, No. 2. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

ENTRY DATE: Entered STN: 18 Jul 2001
Last Updated on STN: 19 Feb 2002

AB The disclosure describes the purification and isolation of a novel human protein Z-dependent protease **inhibitor** (**ZPI**) from **plasma** characterized as having a molecular weight of about 72 kDa, being a single chain protein with an N-terminal amino acid sequence of LAPSPQSPETPA, and which produces a rapid **inhibition** of factor Xa in the presence of human protein Z (PZ), calcium ions and cephalin. The disclosure further describes the isolation and cloning of the **ZPI** cDNA from a human cDNA library. The **ZPI** cDNA is 2.44 kb in length and has an open reading frame that encodes the 423 residue mature **ZPI** protein and a 21 residue signal peptide. PZ, **ZPI** and the combination of PZ and **ZPI** are used to **inhibit blood coagulation**.

L14 ANSWER 7 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 2

ACCESSION NUMBER: 2001170421 EMBASE
TITLE: Mouse protein Z-dependent protease **inhibitor** cDNA.
AUTHOR: Zhang J.; Broze G.J. Jr.
CORPORATE SOURCE: G.J. Broze Jr., Division of Hematology, Mail Zone 90-20-662, Barnes-Jewish Hospital, 216 South Kingshighway Blvd, St. Louis, MO 63110, United States. gbroze@im.wustl.edu
SOURCE: Thrombosis and Haemostasis, (2001) 85/5 (861-865).
Refs: 8
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
030 Pharmacology
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Protein Z-dependent protease **inhibitor** (**ZPI**) is **plasma** proteinase **inhibitor** in the serpin superfamily that produces rapid **inhibition** of factor Xa in the presence of phospholipids, Ca(++) and protein Z (PZ). Mouse **ZPI** cDNA was isolated and cloned from mouse liver RNA using RT-PCR. The cDNA contains 100 nucleotides 5' of a translation initiation codon and an open reading frame of 1344 nucleotides followed by a 163 nucleotide 3' untranslated sequence with a poly (A) tail. The cDNA predicts a signal peptide containing 21 amino acids and a mature protein of 427 residues with 8 potential sites for N-linked glycosylation. The oligonucleotide and predicted amino acid sequences of mouse **ZPI** are 72% and 81% homologous with those of human **ZPI**. Like human **ZPI**, mouse **ZPI** contains tyrosine-serine (P(1)-P(1)') at its reactive center in contrast to the rat molecule which contains tyrosine-cysteine. By Northern analysis, mouse **ZPI** mRNA is 1.6 kb in size and, similar to both human and rat, it is detectable in liver, but not in heart, brain, spleen, lung, kidney, skeletal muscle or testes.

L14 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:261416 BIOSIS
DOCUMENT NUMBER: PREV200200261416
TITLE: Heritability of **clotting** factors, **coagulation inhibitors** and activation peptides.
AUTHOR(S): Rosendaal, Frits R. [Reprint author]; Hasstedt, Sandra J.;

Bauer, Kenneth; Broze, George J.; Long, George L.; Scott, Bruce T.; Callas, Peter W.; Bovill, Edwin G.
CORPORATE SOURCE: Clinical Epidemiology and Hematology, Leiden University Medical Center, Leiden, Netherlands
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 789a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002

AB High levels of several **clotting** factors have been associated with an increased thrombotic risk. These levels may be genetically determined (by quantitaive trait loci). We investigated the contribution of genetic factors to the levels of procoagulant factors, anticoagulant factors and activation peptides. We used **blood** samples collected in an ongoing study of a large kindred with protein C deficiency, living in the North-eastern United States. **Blood** samples were collected over a time frame of 15 years, numbers of individuals per assay vary. Assays were performed by ELISA except FPA (RIA, Mallincrodt Inc.) and FVIII (one-stage **clotting** assay). We excluded individuals using coumarins (for PC, PS, PZ, **ZPI**), who were pregnant (for PS, FVIII), with protein C deficiency (for PC) and with G20210A (for FII). Each variable was transformed to normality and adjusted for age and sex. Factor VIII was adjusted for ABO **blood** group and vWF. Heritability, the proportion of the variance attributed to polygenes, was estimated for each variable using PAP (Hasstedt 2001). Levels of several procoagulant factors (FV, FVIII) and anticoagulant factors (AT, PC, PS) had heritabilities between 30 and 60 percent. Activation of protein C, as indicated by PCP, and APC-**inhibitor** complexes, had a high heritability (36-77 percent), while both levels of prothrombin and prothrombin activation had not.

L14 ANSWER 9 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3
ACCESSION NUMBER: 2001139693 EMBASE
TITLE: Protein Z circulates in **plasma** in a complex with protein Z-dependent protease **inhibitor**.
AUTHOR: Tabatabai A.; Fiehler R.; Broze G.J. Jr.
CORPORATE SOURCE: Dr. G.J. Broze Jr., Division of Hematology, Barnes-Jewish Hospital, 216 S. Kingshighway Blvd., St. Louis, MO 63110, United States. gbroze@im.wustl.edu
SOURCE: Thrombosis and Haemostasis, (2001) 85/4 (655-660).
Refs: 31
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Protein Z (PZ) is a vitamin K-dependent **plasma** protein that forms a Ca(++)-dependent complex with factor Xa at phospholipid surfaces. This interaction between PZ and factor Xa enhances by > 1000-fold the **inhibition** of factor Xa by the serpin called protein Z-dependent protease **inhibitor** (**ZPI**). These experiments show that PZ also binds **ZPI** in a process that does not require Ca(++) or phospholipids. In pooled normal **plasma**, which contains excess

ZPI relative to PZ, all the PZ appears to be bound in a complex with **ZPI**. The binding of PZ to **ZPI** reduces the rate and extent of factor XIa **inhibition** produced by **ZPI**. During the course of these studies, it was noted that a PZ purification procedure, that included NaSCN (2.0 M) elution of PZ from an immunoaffinity column, produced aggregated, inactive forms of PZ.

L14 ANSWER 10 OF 15 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001440927 MEDLINE
DOCUMENT NUMBER: 21379114 PubMed ID: 11487045
TITLE: Protein Z-dependent regulation of **coagulation**.
AUTHOR: Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, MO 63110, USA.. gbroze@im.wustl.edu
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Jul) 86 (1) 8-13. Ref: 47
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Protein Z (PZ) is a 62 kDa vitamin K-dependent **plasma** protein that serves as a cofactor for the **inhibition** of factor Xa by protein Z-dependent protease **inhibitor** (**ZPI**). **ZPI** is a recently identified 72 kDa member of the serpin superfamily of proteinase **inhibitors** that contains a tyrosine at its reactive center. PZ circulates in **plasma** in a complex with **ZPI**. **Inhibition** of factor Xa by **ZPI** in the presence of phospholipids and Ca++ is enhanced 1000-fold by PZ, but **ZPI** also **inhibits** factor XIa in a process that does not require PZ, phospholipids or Ca++. **ZPI** activity is consumed during **coagulation** through proteolysis mediated by factor Xa with PZ and factor Xla. Concomitant PZ deficiency dramatically increases the severity of the prothrombotic phenotype of factor VLeiden mice. Studies to determine the potential roles of PZ and **ZPI** deficiency in human thrombosis are in progress.

L14 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001051375 MEDLINE
DOCUMENT NUMBER: 20504046 PubMed ID: 11049983
TITLE: Characterization of the protein Z-dependent protease **inhibitor**.
AUTHOR: Han X; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University Medical Center, St Louis, MO 63110, USA.
SOURCE: BLOOD, (2000 Nov 1) 96 (9) 3049-55.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322

Entered Medline: 20001211

AB Protein Z-dependent protease **inhibitor** (**ZPI**) is a 72-kd member of the serpin superfamily of proteinase **inhibitors** that produces rapid **inhibition** of factor Xa in the presence of protein Z (PZ), procoagulant phospholipids, and Ca(++) (t(1/2) less than 10 seconds). The rate of factor Xa **inhibition** by **ZPI** is reduced more than 1000-fold in the absence of PZ. The factor Xa-**ZPI** complex is not stable to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, but is detectable by alkaline-polyacrylamide gel electrophoresis. The combination of PZ and **ZPI** dramatically delays the initiation and reduces the ultimate rate of thrombin generation in mixtures containing prothrombin, factor V, phospholipids, and Ca(++). In similar mixtures containing factor Va, however, PZ and **ZPI** do not **inhibit** thrombin generation. Thus, the major effect of PZ and **ZPI** is to dampen the **coagulation** response prior to the formation of the prothrombinase complex. Besides factor Xa, **ZPI** also **inhibits** factor XIa in the absence of PZ, phospholipids, and Ca(++). Heparin (0.2 U/mL) enhances the rate (t(1/2) = 25 seconds vs 50 seconds) and the extent (99% vs 93% at 30 minutes) of factor XIa **inhibition** by **ZPI**. During its **inhibitory** interaction with factor Xa and factor XIa, **ZPI** is proteolytically cleaved with the release of a 4.2-kd peptide. The N-terminal amino acid sequence of this peptide (SMPPVIKVDRPF) establishes Y387 as the P(1) residue at the reactive center of **ZPI**. **ZPI** activity is consumed during the in vitro **coagulation** of **plasma** through a proteolytic process that involves the actions of factor Xa with PZ and factor XIa.

L14 ANSWER 12 OF 15 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2000-02957 BIOTECHDS
TITLE: New isolated human protein Z-dependent protease-**inhibitor**, used for **inhibiting** Factor-Xa, particularly for **inhibiting blood coagulation**; recombinant Factor-Xa-**inhibitor** with anticoagulant and thrombolytic activity
AUTHOR: Broze Jr G J
PATENT ASSIGNEE: Univ.Washington
LOCATION: St. Louis, MO, USA.
PATENT INFO: WO 9960126 25 Nov 1999
APPLICATION INFO: WO 1999-US7040 13 May 1999
PRIORITY INFO: US 1998-86571 19 May 1998
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2000-062457 [05]

AB Human protein-Z-dependent protease-**inhibiting** (**ZPI**) (A) with a mol.wt. of 72,000, an N-terminal amino acid sequence of 12 residues (disclosed), and **inhibits** Factor-Xa in the presence of protein-Z, calcium ions and cephalin, is claimed. (A) is a single chain protein that gives a rapid **inhibition** of Factor-Xa in the presence of protein-Z, calcium ions and cephalin. Also claimed are: a DNA molecule comprising a sequence encoding a protein sequence of 423 amino acids (disclosed); a **ZPI** with a disclosed 423 amino acid protein sequence; a method for **inhibiting blood coagulation** involving administering protein-Z and/or **ZPI**; and a method for **inhibiting** Factor-Xa in serum or **plasma** comprising contacting the serum or **plasma** with an **inhibitor** as in (A) or a protein of 423 amino acids. The Factor-Xa-**inhibitor** has anticoagulant and thrombolytic activity. The **ZPI** can be used for **inhibiting** Factor-Xa in serum or **plasma**. A DNA sequence of 2,466 bp is disclosed. (54pp)

L14 ANSWER 13 OF 15 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999389569 MEDLINE
DOCUMENT NUMBER: 99389569 PubMed ID: 10460162
TITLE: The protein Z-dependent protease **inhibitor** is a serpin.
AUTHOR: Han X; Huang Z F; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: HL-60782 (NHLBI)
SOURCE: BIOCHEMISTRY, (1999 Aug 24) 38 (34) 11073-8. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF181467
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990923

AB In the presence of phospholipid vesicles and calcium ions, protein Z (PZ) serves as a cofactor for the **inhibition** of **coagulation** factor Xa by a **plasma** protein called PZ-dependent protease **inhibitor** (**ZPI**). To further characterize **ZPI**, its cDNA has been isolated and cloned from a human liver cDNA library. The **ZPI** cDNA is 2.44 kb in length and has a relatively long 5' region (466 nt) that contains six potential ATG translation start codons. ATG's 1-4 are followed by short open reading frames, whereas ATG(5) and ATG(6) are in an uninterrupted open reading frame that includes the encoded **ZPI** protein. In vitro experiments show that ATG(6) is sufficient for the expression of rZPI in cultured Chinese hamster ovary cells. Northern analysis suggests the liver is a major site of **ZPI** synthesis. The predicted 423 residue amino acid sequence of the mature **ZPI** protein is 25-35% homologous with members of the serpin superfamily of protease **inhibitors** and is 78% identical to the amino acid sequence predicted by a previously described cDNA isolated from rat liver, regeneration-associated serpin protein-1 (rasp-1). Thus, **ZPI** is likely the human homologue of rat rasp-1. Alignment of the amino acid sequence of **ZPI** with those of other serpins predicts that Y387 is the P(1) residue at the reactive center of the **ZPI** molecule. Consistent with this notion, rZPI(Y387A), an altered form of **ZPI** in which tyrosine 387 has been changed to alanine, lacks PZ-dependent factor Xa **inhibitory** activity.

L14 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998356143 MEDLINE
DOCUMENT NUMBER: 98356143 PubMed ID: 9689066
TITLE: Isolation of a protein Z-dependent **plasma** protease **inhibitor**.
AUTHOR: Han X; Fiehler R; Broze G J Jr
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, 216 South Kingshighway Boulevard, St. Louis, MO 63110, USA.
CONTRACT NUMBER: HL34462 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Aug 4) 95 (16) 9250-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980908

AB Human protein Z (PZ) is a 62,000-Mr, vitamin K-dependent **plasma** protein whose structure is similar to **coagulation** factors VII, IX, X, protein C, and protein S, but whose function is not known. The procoagulant activity of factor Xa in a one-stage **plasma coagulation** assay is reduced when factor Xa is first incubated with PZ. This apparent **inhibitory** effect is time dependent, requires the presence of calcium ions and procoagulant phospholipids (rabbit brain cephalin), and appears predominantly related to the incubation period of PZ with cephalin. In serum the initial rate of **inhibition** of factor Xa with calcium ions and cephalin also is enhanced in the presence PZ. A PZ-dependent protease **inhibitor** (**ZPI**) has been isolated from **plasma**. **ZPI** is a 72,000-Mr single-chain protein with an N-terminal amino acid sequence of LAPSPQSPEXXA (X = indeterminate) and an estimated concentration in citrate-treated **plasma** of 1.0-1.6 microg/ml. In systems using purified components, the factor Xa **inhibition** produced by **ZPI** is rapid (>95% within 1 min by **coagulation** assay) and requires the presence of PZ, calcium ions, and cephalin. The **inhibitory** process appears to involve the formation of a factor Xa-PZ-**ZPI** complex at the phospholipid surface.

L14 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:531521 HCAPLUS
DOCUMENT NUMBER: 119:131521
TITLE: Polypeptide composition for stimulating vascular endothelial cell growth and **inhibiting blood coagulation**
INVENTOR(S): Kitaguchi, Nobuya; Aratake, Takashi; Tokushima, Yasuo
PATENT ASSIGNEE(S): Asahi Chemical Industry Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 04327538	A2	19921117	JP 1991-97126	19910426

PRIORITY APPLN. INFO.: JP 1991-97126 19910426

AB A polypeptide capable of stimulating vascular endothelial cell growth and **inhibiting blood coagulation** is provided. The compn. is useful in treatment of cardiovascular diseases, burns, ulcer, etc. The polypeptide is derived from the protease-**inhibiting** region APPI of Alzheimer disease-related glycoproteins APP. The core region, KPI, for the protease **inhibitor** activity of APP751 and APP770 also exhibits the vascular endothelial cell growth-stimulating activity. The KPI was expressed in COS cells or Escherichia coli as a single or chimeric protein for mass prodn. and its biol. activities obsd.

=> d his

(FILE 'HOME' ENTERED AT 14:11:06 ON 21 OCT 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,

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     LIFESCI' ENTERED AT 14:11:28 ON 21 OCT 2003
L1       9134759 S BLOOD? OR PLASMA
L2        553896 S CLOT? OR COAGULAT?
L3        290216 S L1 AND L2
L4           950 S "PROTEIN Z"
L5         20233 S "FACTOR XA"
L6            76 S L4 AND L5
L7            99 S "PROTEIN Z INHIBITOR" OR "ZPI"
L8            56 S HUMAN AND L7
L9            40 S L8 AND L5
L10           30 S L3 AND L9
L11           13 DUP REM L10 (17 DUPLICATES REMOVED)
L12        81541 S L3 AND (PROLONG? OR INHIBIT?)
L13           35 S L7 AND L12
L14           15 DUP REM L13 (20 DUPLICATES REMOVED)

=> e broze G j/au
E1             1     BROZE ELLERT R/AU
E2           126     BROZE G/AU
E3           161 --> BROZE G J/AU
E4           211     BROZE G J JR/AU
E5             1     BROZE G J JR */AU
E6             4     BROZE G JR/AU
E7             6     BROZE GEORGE/AU
E8            19     BROZE GEORGE J/AU
E9           131     BROZE GEORGE J JR/AU
E10            3     BROZE GEORGE JOHN JR/AU
E11            2     BROZE GEORGE JR/AU
E12          151     BROZE GUY/AU

=> s e3-e5
L15          373 ("BROZE G J"/AU OR "BROZE G J JR"/AU OR "BROZE G J JR *"/AU)

=> s l7 and l15
L16           21 L7 AND L15

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17            7 DUP REM L16 (14 DUPLICATES REMOVED)

=> d 1-7 ibib ab

L17  ANSWER 1 OF 7     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2003377646     IN-PROCESS
DOCUMENT NUMBER:    22794934   PubMed ID: 12911591
TITLE:              Autoimmune antiphospholipid antibodies impair the
                    inhibition of activated factor X by protein Z/protein
                    Z-dependent protease inhibitor.
AUTHOR:             Forastiero R R; Martinuzzo M E; Lu L; Broze G J
CORPORATE SOURCE:   Division of Haematology, Thrombosis and Haemostasis,
                    Favaloro University, Favaloro Foundation, Buenos Aires,
                    Argentina.
SOURCE:             J Thromb Haemost, (2003 Aug) 1 (8) 1764-70.
                    Journal code: 101170508. ISSN: 1538-7933.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20030813
                    Last Updated on STN: 20030813
AB   The hemostatic process is tightly regulated by several antithrombotic
     mechanisms.  Among them, protein Z (PZ)-dependent protease inhibitor (
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ZPI) potently inhibits factor (F)Xa in a manner dependent on calcium ions, phospholipids and PZ. Autoimmune antiphospholipid antibodies (aPL) are mainly directed against phospholipid-binding plasma proteins such as beta2-glycoprotein I (beta2GPI) and prothrombin, and are known to interfere with phospholipid-dependent hemostatic pathways. In this study, we investigated whether purified aPL are able to interfere with inhibition of FXa by PZ/**ZPI**. beta2GPI modestly delayed the FXa inactivation by PZ/**ZPI** and most isolated aPL-IgGs were found to further increase the inhibitory potential of beta2GPI on PZ/**ZPI** activity. Without beta2GPI, the PZ/**ZPI** activity was unaffected by the addition of aPL-IgG. As PZ deficiency is hypothesized to lead to a prothrombotic state, we performed a case-control study to measure plasma levels of PZ and **ZPI** in 66 patients with autoimmune aPL and 152 normal controls. The prevalence of low PZ levels (below the 5th percentile of controls) was significantly greater in the 37 patients with definite antiphospholipid syndrome (APS) (24.3%) but not in the 29 aPL patients not fulfilling the criteria for APS (10.3%) compared with the normal group (4.6%, P < 0.001 vs. APS). **ZPI** antigen levels were similar in patients with aPL and normal controls. Concomitant PZ deficiency increased by approximately sevenfold the risk of arterial thrombosis in aPL patients. Taken together, these data suggest that the PZ/**ZPI** system is commonly impaired in aPL patients thus probably increasing the thrombotic risk.

L17 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002010424 MEDLINE
DOCUMENT NUMBER: 21265570 PubMed ID: 11372680
TITLE: Mouse protein Z-dependent protease inhibitor cDNA.
AUTHOR: Zhang J; **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University Medical Center, St Louis, MO 63110, USA.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 May) 85 (5) 861-5. Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020220
Entered Medline: 20020219

AB Protein Z-dependent protease inhibitor (**ZPI**) is plasma proteinase inhibitor in the serpin superfamily that produces rapid inhibition of factor Xa in the presence of phospholipids, Ca++ and protein Z (PZ). Mouse **ZPI** cDNA was isolated and cloned from mouse liver RNA using RT-PCR. The cDNA contains 100 nucleotides 5' of a translation initiation codon and an open reading frame of 1344 nucleotides followed by a 163 nucleotide 3' untranslated sequence with a poly (A) tail. The cDNA predicts a signal peptide containing 21 amino acids and a mature protein of 427 residues with 8 potential sites for N-linked glycosylation. The oligonucleotide and predicted amino acid sequences of mouse **ZPI** are 72% and 81% homologous with those of human **ZPI**. Like human **ZPI**, mouse **ZPI** contains tyrosine-serine (P1-P1') at its reactive center in contrast to the rat molecule which contains tyrosine-cysteine. By Northern analysis, mouse **ZPI** mRNA is 1.6 kb in size and, similar to both human and rat, it is detectable in liver, but not in heart, brain, spleen, lung, kidney, skeletal muscle or testes.

L17 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002009330 MEDLINE
DOCUMENT NUMBER: 21239115 PubMed ID: 11341501

TITLE: Protein Z circulates in plasma in a complex with protein Z-dependent protease inhibitor.
AUTHOR: Tabatabai A; Fiehler R; **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University Medical Center, St Louis, MO 63110, USA.
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Apr) 85 (4) 655-60.
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011204

AB Protein Z (PZ) is a vitamin K-dependent plasma protein that forms a Ca++-dependent complex with factor Xa at phospholipid surfaces. This interaction between PZ and factor Xa enhances by >1,000-fold the inhibition of factor Xa by the serpin called protein Z-dependent protease inhibitor (**ZPI**). These experiments show that PZ also binds **ZPI** in a process that does not require Ca++ or phospholipids. In pooled normal plasma, which contains excess **ZPI** relative to PZ, all the PZ appears to be bound in a complex with **ZPI**. The binding of PZ to **ZPI** reduces the rate and extent of factor XIa inhibition produced by **ZPI**. During the course of these studies, it was noted that a PZ purification procedure, that included NaSCN (2.0 M) elution of PZ from an immunoaffinity column, produced aggregated, inactive forms of PZ.

L17 ANSWER 4 OF 7 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001440927 MEDLINE
DOCUMENT NUMBER: 21379114 PubMed ID: 11487045
TITLE: Protein Z-dependent regulation of coagulation.
AUTHOR: **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital, Washington University School of Medicine, St. Louis, MO 63110, USA.. gbroze@im.wustl.edu
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Jul) 86 (1) 8-13. Ref: 47
Journal code: 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Protein Z (PZ) is a 62 kDa vitamin K-dependent plasma protein that serves as a cofactor for the inhibition of factor Xa by protein Z-dependent protease inhibitor (**ZPI**). **ZPI** is a recently identified 72 kDa member of the serpin superfamily of proteinase inhibitors that contains a tyrosine at its reactive center. PZ circulates in plasma in a complex with **ZPI**. Inhibition of factor Xa by **ZPI** in the presence of phospholipids and Ca++ is enhanced 1000-fold by PZ, but **ZPI** also inhibits factor XIa in a process that does not require PZ, phospholipids or Ca++. **ZPI** activity is consumed during coagulation through proteolysis mediated by factor Xa with PZ and factor Xla. Concomitant PZ deficiency dramatically increases

the severity of the prothrombotic phenotype of factor VLeiden mice. Studies to determine the potential roles of PZ and **ZPI** deficiency in human thrombosis are in progress.

L17 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001051375 MEDLINE
DOCUMENT NUMBER: 20504046 PubMed ID: 11049983
TITLE: Characterization of the protein Z-dependent protease inhibitor.
AUTHOR: Han X; Fiehler R; **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University Medical Center, St Louis, MO 63110, USA.
SOURCE: BLOOD, (2000 Nov 1) 96 (9) 3049-55.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001211

AB Protein Z-dependent protease inhibitor (**ZPI**) is a 72-kd member of the serpin superfamily of proteinase inhibitors that produces rapid inhibition of factor Xa in the presence of protein Z (PZ), procoagulant phospholipids, and Ca(++) (t(1/2) less than 10 seconds). The rate of factor Xa inhibition by **ZPI** is reduced more than 1000-fold in the absence of PZ. The factor Xa-**ZPI** complex is not stable to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, but is detectable by alkaline-polyacrylamide gel electrophoresis. The combination of PZ and **ZPI** dramatically delays the initiation and reduces the ultimate rate of thrombin generation in mixtures containing prothrombin, factor V, phospholipids, and Ca(++). In similar mixtures containing factor Va, however, PZ and **ZPI** do not inhibit thrombin generation. Thus, the major effect of PZ and **ZPI** is to dampen the coagulation response prior to the formation of the prothrombinase complex. Besides factor Xa, **ZPI** also inhibits factor XIa in the absence of PZ, phospholipids, and Ca(++). Heparin (0.2 U/mL) enhances the rate (t(1/2) = 25 seconds vs 50 seconds) and the extent (99% vs 93% at 30 minutes) of factor XIa inhibition by **ZPI**. During its inhibitory interaction with factor Xa and factor XIa, **ZPI** is proteolytically cleaved with the release of a 4.2-kd peptide. The N-terminal amino acid sequence of this peptide (SMPPVIKVDRPF) establishes Y387 as the P(1) residue at the reactive center of **ZPI**. **ZPI** activity is consumed during the in vitro coagulation of plasma through a proteolytic process that involves the actions of factor Xa with PZ and factor XIa.

L17 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999389569 MEDLINE
DOCUMENT NUMBER: 99389569 PubMed ID: 10460162
TITLE: The protein Z-dependent protease inhibitor is a serpin.
AUTHOR: Han X; Huang Z F; Fiehler R; **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: HL-60782 (NHLBI)
SOURCE: BIOCHEMISTRY, (1999 Aug 24) 38 (34) 11073-8.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF181467
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990923

AB In the presence of phospholipid vesicles and calcium ions, protein Z (PZ) serves as a cofactor for the inhibition of coagulation factor Xa by a plasma protein called PZ-dependent protease inhibitor (**ZPI**). To further characterize **ZPI**, its cDNA has been isolated and cloned from a human liver cDNA library. The **ZPI** cDNA is 2.44 kb in length and has a relatively long 5' region (466 nt) that contains six potential ATG translation start codons. ATG's 1-4 are followed by short open reading frames, whereas ATG(5) and ATG(6) are in an uninterrupted open reading frame that includes the encoded **ZPI** protein. In vitro experiments show that ATG(6) is sufficient for the expression of rZPI in cultured Chinese hamster ovary cells. Northern analysis suggests the liver is a major site of **ZPI** synthesis. The predicted 423 residue amino acid sequence of the mature **ZPI** protein is 25-35% homologous with members of the serpin superfamily of protease inhibitors and is 78% identical to the amino acid sequence predicted by a previously described cDNA isolated from rat liver, regeneration-associated serpin protein-1 (rasp-1). Thus, **ZPI** is likely the human homologue of rat rasp-1. Alignment of the amino acid sequence of **ZPI** with those of other serpins predicts that Y387 is the P(1) residue at the reactive center of the **ZPI** molecule. Consistent with this notion, rZPI(Y387A), an altered form of **ZPI** in which tyrosine 387 has been changed to alanine, lacks PZ-dependent factor Xa inhibitory activity.

L17 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998356143 MEDLINE
DOCUMENT NUMBER: 98356143 PubMed ID: 9689066
TITLE: Isolation of a protein Z-dependent plasma protease inhibitor.
AUTHOR: Han X; Fiehler R; **Broze G J Jr**
CORPORATE SOURCE: Division of Hematology, Barnes-Jewish Hospital at Washington University School of Medicine, 216 South Kingshighway Boulevard, St. Louis, MO 63110, USA.
CONTRACT NUMBER: HL34462 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Aug 4) 95 (16) 9250-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980908

AB Human protein Z (PZ) is a 62,000-Mr, vitamin K-dependent plasma protein whose structure is similar to coagulation factors VII, IX, X, protein C, and protein S, but whose function is not known. The procoagulant activity of factor Xa in a one-stage plasma coagulation assay is reduced when factor Xa is first incubated with PZ. This apparent inhibitory effect is time dependent, requires the presence of calcium ions and procoagulant phospholipids (rabbit brain cephalin), and appears predominantly related to the incubation period of PZ with cephalin. In serum the initial rate of inhibition of factor Xa with calcium ions and cephalin also is enhanced in the presence PZ. A PZ-dependent protease inhibitor (**ZPI**) has

been isolated from plasma. **ZPI** is a 72,000-Mr single-chain protein with an N-terminal amino acid sequence of LAPSPQSPEXXA (X = indeterminate) and an estimated concentration in citrate-treated plasma of 1.0-1.6 microg/ml. In systems using purified components, the factor Xa inhibition produced by **ZPI** is rapid (>95% within 1 min by coagulation assay) and requires the presence of PZ, calcium ions, and cephalin. The inhibitory process appears to involve the formation of a factor Xa-PZ-**ZPI** complex at the phospholipid surface.

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(FILE 'HOME' ENTERED AT 14:11:06 ON 21 OCT 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:11:28 ON 21 OCT 2003

L1	9134759	S	BLOOD? OR PLASMA
L2	553896	S	CLOT? OR COAGULAT?
L3	290216	S	L1 AND L2
L4	950	S	"PROTEIN Z"
L5	20233	S	"FACTOR XA"
L6	76	S	L4 AND L5
L7	99	S	"PROTEIN Z INHIBITOR" OR "ZPI"
L8	56	S	HUMAN AND L7
L9	40	S	L8 AND L5
L10	30	S	L3 AND L9
L11	13	DUP REM	L10 (17 DUPLICATES REMOVED)
L12	81541	S	L3 AND (PROLONG? OR INHIBIT?)
L13	35	S	L7 AND L12
L14	15	DUP REM	L13 (20 DUPLICATES REMOVED)
		E	BROZE G J/AU
L15	373	S	E3-E5
L16	21	S	L7 AND L15
L17	7	DUP REM	L16 (14 DUPLICATES REMOVED)

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	Issue Date	Pages	Document ID	Title
1	20030904	36	US 20030166147 A1	Clonal myeloma cell lines useful for manufacturing proteins in chemically defined media
2	20030904	34	US 20030166146 A1	Myeloma cell line useful for manufacturing recombinant proteins in chemically defined media
3	20030807	120	US 20030148295 A1	Expression profiles and methods of use
4	20030724	142	US 20030138795 A1	Polynucleotide encoding a novel human growth factor with homology to epidermal growth factor, BGS-8, expressed highly in immune tissue
5	20030206	14	US 20030027235 A1	Novel method and diagnostic agent for hemostasis diagnosis
6	20021205	27	US 20020183254 A1	Protein Z-dependent protease inhibitor
7	20021119	12	US 6482653 B1	Method and diagnostic agent for hemostasis diagnosis
8	20020723	25	US 6423826 B1	High molecular weight derivatives of vitamin K-dependent polypeptides
9	20020409	25	US 6369031 B1	Protein Z-dependent protease inhibitor
10	20010828	15	US 6280727 B1	Compositions containing thrombin and microfibrillar collagen and methods for preparation and use thereof
11	20010807	26	US 6271367 B1	Protein Z-dependent protease inhibitor
12	20010724	25	US 6265378 B1	Protein Z-dependent protease inhibitor
13	20010612	26	US 6245741 B1	Protein Z-dependent protease inhibitor

	Issue Date	Pages	Document ID	Title
14	20010213	15	US 6187594 B1	Method and diagnostic agent for hemostasis diagnosis
15	20000801	14	US 6096309 A	Compositions containing thrombin and microfibrillar nanometer collagen, and methods for preparation and use thereof
16	20000125	12	US 6017891 A	Stable preparation for the treatment of blood coagulation disorders

	Issue Date	Pages	Document ID	Title
1	20021205	27	US 20020183254 A1	Protein Z-dependent protease inhibitor
2	20020409	25	US 6369031 B1	Protein Z-dependent protease inhibitor
3	20010807	26	US 6271367 B1	Protein Z-dependent protease inhibitor
4	20010724	25	US 6265378 B1	Protein Z-dependent protease inhibitor
5	20010612	26	US 6245741 B1	Protein Z-dependent protease inhibitor

	Issue Date	Pages	Document ID	Title
1	20030911	29	US 20030171292 A1	Method for using lipoprotein associated coagulation inhibitor to treat sepsis
2	20030904	15	US 20030166194 A1	DNA clone of human tissue factor inhibitor
3	20030515	7	US 20030092593 A1	Superior surfactant system for laundry detergent composition based on alkyl benzene sulfonate and ethylene oxide/propylene oxide copolymer
4	20021205	27	US 20020183254 A1	Protein Z-dependent protease inhibitor
5	20020919	26	US 20020132749 A1	Thickened fabric conditioners
6	20020425	8	US 20020049149 A1	All purpose liquid cleaning compositions
7	20011213	9	US 20010051596 A1	Chemical linker compositions
8	20010816	9	US 20010014654 A1	Chemical linker compositions
9	20030902	6	US 6613730 B1	Liquid cleaning compositions
10	20030819	8	US 6608020 B1	Liquid cleaning compositions
11	20030812	7	US 6605585 B1	Liquid cleaning compositions
12	20030318	7	US 6534470 B1	Liquid cleaning compositions

	Issue Date	Pages	Document ID	Title
13	20030318	9	US 6534469 B1	Liquid cleaning compositions
14	20030318	8	US 6534468 B1	Liquid cleaning compositions
15	20030318	16	US 6534276 B1	Methods for detecting human tissue factor inhibitor
16	20030311	9	US 6531442 B1	Liquid cleaning compositions comprising fluoroalkyl sulfonate
17	20020716	8	US 6420325 B2	Chemical linker compositions
18	20020604	7	US 6399563 B1	All purpose liquid cleaning compositions
19	20020521	10	US 6391843 B1	Chemical linker compositions

	Issue Date	Pages	Document ID	Title
20	20020521	7	US 6391841 B1	All purpose liquid cleaning compositions
21	20020430	6	US 6380150 B1	Light duty liquid composition containing gelatin beads and polyacrylate thickener
22	20020409	25	US 6369031 B1	Protein Z-dependent protease inhibitor
23	20020409	8	US 6369013 B1	Liquid detergent compositions
24	20020326	6	US 6362148 B1	Anti-lime scale cleaning composition comprising polyoxyethylene oxide polycarboxylic acid copolymer
25	20020212	8	US 6346508 B1	Acidic all purpose liquid cleaning compositions
26	20020129		US 6342475 B1	Liquid cleaning compositions
27	20020115		US 6339058 B1	Light duty liquid composition containing gelatin beads and polyacrylate thickener
28	20020108		US 6337311 B1	All purpose liquid cleaning compositions
29	20011023		US 6306809 B1	Chemical linker compositions
30	20011016		US 6303555 B1	Chemical linker compositions

	Issue Date	Pages	Document ID	Title
31	20010807	26	US 6271367 B1	Protein Z-dependent protease inhibitor
32	20010724	25	US 6265378 B1	Protein Z-dependent protease inhibitor
33	20010612	26	US 6245741 B1	Protein Z-dependent protease inhibitor
34	20010605		US 6242401 B1	All purpose liquid cleaning compositions
35	20010306		US 6197741 B1	Chemical linker compositions
36	20010306		US 6197732 B1	Chemical linker compositions
37	20010213		US 6187735 B1	Light duty liquid detergent

	Issue Date	Pages	Document ID	Title
38	20010130		US 6180582 B1	Liquid cleaning compositions
39	20010123		US 6177394 B1	All purpose liquid cleaning compositions
40	20010109		US 6172032 B1	Chemical linker compositions
41	20010109		US 6171587 B1	Antibodies to tissue factor inhibitor
42	20001121		US 6150321 A	Chemical linker compositions

	Issue Date	Pages	Document ID	Title
43	20001031		US 6140288 A	All purpose liquid cleaning compositions
44	20001024		US 6137728 A	Nonvolatile reprogrammable interconnect cell with programmable buried source/drain in sense transistor
45	20000606		US 6072720 A	Nonvolatile reprogrammable interconnect cell with programmable buried bitline
46	20000516		US 6063764 A	Method for using lipoprotein associated coagulation inhibitor to treat sepsis
47	20000411		US 6048835 A	Animal and/or vegetable protein containing cleaning compositions
48	20000328		US 6043208 A	All purpose liquid cleaning compositions
49	20000215		US 6025316 A	Detergent composition having improved cleaning power

	Issue Date	Pages	Document ID	Title
50	20000208		US 6022839 A	All purpose liquid cleaning compositions
51	20000201		US 6020301 A	Chemical linker compositions
52	19991130		US 5994283 A	Liquid cleaning compositions comprising a negatively charged complex of an anionic and zwitterionic surfactant
53	19990928		US 5958861 A	Liquid cleaning compositions containing a Lewis neutral base polymer

	Issue Date	Pages	Document ID	Title
54	19990921		US 5955407 A	Chemical linker compositions
55	19990914		US 5952288 A	Protein containing cleaning compositions
56	19990907		US 5948745 A	Detergent composition having improved cleaning power
57	19990817		US 5939376 A	Liquid cleaning compositions containing an organic ester foam control agent
58	19990727		US 5929023 A	Cleaning composition containing a N-octyl ribonamide

	Issue Date	Pages	Document ID	Title
59	19990413		US 5894148 A	Floating gate FPGA cell with counter-doped select device
60	19990330		US 5888957 A	Liquid cleaning compositions containing a negatively charged surfactant complex
61	19990330		US 5888956 A	Liquid cleaning composition consisting essentially of a negatively charged complex of an anionic surfactant and an amine oxide or alkylene carbonate
62	19990119		US 5861367 A	Cleaning and disinfecting composition in microemulsion/liquid crystal form comprising aldehyde and mixture of partially esterified, fully esterified and non-esterified polyhydric alcohols

	Issue Date	Pages	Document ID	Title
63	19981229		US 5854194 A	Chemical linker compositions
64	19981222		US 5851971 A	Liquid cleaning compositions
65	19981215		US 5849875 A	Human tissue factor inhibitor
66	19981117		US 5838040 A	Nonvolatile reprogrammable interconnect cell with FN tunneling in sense
67	19981110		US 5834413 A	Liquid cleaning compositions
68	19980825		US 5798330 A	Liquid cleaning compositions

	Issue Date	Pages	Document ID	Title
69	19980630		US 5773251 A	DNA clone of human tissue factor inhibitor
70	19980623		US 5770554 A	Liquid cleaning compositions
71	19980609		US 5764096 A	General purpose, non-volatile reprogrammable switch
72	19980609		US 5763386 A	Microemulsion all purpose liquid cleaning compositions comprising ethoxylated polyhydric alcohols with at least partial esters thereof, and optional dralkyl sulfosuccinate
73	19980512		US 5750487 A	Tricritical point compositions
74	19980407		US 5736496 A	Liquid cleaning compositions comprising a negatively charged complex comprising an anionic surfactant and an alkylene carbonate

	Issue Date	Pages	Document ID	Title
75	19980331		US 5733860 A	Alkylene carbonated and their preparation
76	19980331		US 5733560 A	Method of improving retention time of volatile organic chemical coated on a surface
77	19980324		US 5731281 A	Microemulsion liquid crystal cleaning compositions comprising esterified and non-esterfied ethoxylated glycerol mixture and sulfoxy anionic surfactant
78	19980317		US 5728668 A	Cleaning composition
79	19970909		US 5665268 A	Near tricritical point compositions
80	19970722		US 5650391 A	Methods and compositions for inhibition of hepatic clearance of tissue factor pathway inhibitor
81	19970527		US 5633518 A	Nonvolatile reprogrammable interconnect cell with FN tunneling and programming method thereof
82	19970401		US 5616548 A	Stable microemulsion cleaning composition
83	19970218		US 5604195 A	Liquid cleaning compositions with polyethylene glycol grease release agent
84	19970211		US 5602069 A	Glass cleaning composition

	Issue Date	Pages	Document ID	Title
85	19970204		US 5599785 A	Cleaning composition in microemulsion or liquid crystal form comprising mixture of partially esterified, fully esterified and non-esterified polyhydric alchohols
86	19970114		US 5593958 A	Cleaning composition in microemulsion, crystal or aqueous solution form based on ethoxylated polyhydric alcohols and option esters's thereof
87	19961105		US 5571459 A	Microemulsion all purpose liquid cleaning compositions
88	19961015		US 5565419 A	Oven cleaning composition
89	19960827		US 5549840 A	Cleaning composition in microemulsion, liquid crystal or aqueous solution form comprising mixture of partially esterified, full esterified and non-esterified ethoxylated polyhydric alcohols
90	19960618		US 5527485 A	Near tricritical point compositions
91	19960604		US 5523013 A	Liquid crystal compositions
92	19951121		US 5468398 A	Liquid fabric softening composition
93	19951114		US 5466783 A	Human tissue factor inhibitor

	Issue Date	Pages	Document ID	Title
94	19950725		US 5435936 A	Nonaqueous liquid microemulsion compositions
95	19950516		US 5415812 A	Light duty microemulsion liquid detergent composition
96	19950228		US 5393468 A	Hard surface cleaner
97	19950228		US 5393454 A	Thickened composition containing polymeric thickener and aliphatic hydrocarbon
98	19950228		US 5393453 A	Thickened composition containing glycolipid surfactant and polymeric thickener
99	19941220		US 5374372 A	Nonaqueous liquid crystal compositions
100	19920421		US 5106833 A	Coagulation inhibitors

	Issue Date	Pages	Document ID	Title
101	19911015		US 5057238 A	Liquid laundry detergent composition containing polyphosphate
102	19910910		US 5047168 A	Sugar ethers as bleach stable detergency boosters
103	19910730		US 5035826 A	Liquid crystal detergent composition
104	19901030		US 4966852 A	DNA clone of human tissue factor inhibitor
105	19900424		US 4919839 A	Light duty microemulsion liquid detergent composition containing an aniocic/cationic complex
106	19891226		US 4889651 A	Acetylated sugar ethers as bleach activators and detergency boosters
107	19891010		US 4873012 A	Built nonaqueous liquid nonioinic laundry detergent composition containing hexylene glycol and method of use
108	19890516		US 4830782 A	Hot water wash cycle built nonaqueous liquid nonionic laundry detergent composition containing amphoteric surfactant and method of use

	Issue Date	Pages	Document ID	Title
109	19890221		US 4806260 A	Built nonaqueous liquid nonionic laundry detergent composition containing acid terminated nonionic surfactant and quarternary ammonium softener and method of use
110	19890124		US 4800038 A	Acetylated sugar ethers as bleach activators detergency boosters and fabric softeners
111	19890124		US 4800035 A	Liquid laundry detergent composition containing polyphosphate
112	19890110		US 4797225 A	Nonaqueous liquid nonionic laundry detergent composition containing an alkali metal dithionite or sulfite reduction bleaching agent and method of use
113	19881206		US 4789496 A	Built nonaqueous liquid nonionic laundry detergent composition containing
114	19881122		US 4786431 A	Liquid laundry detergent-bleach composition and method of use

	Issue Date	Pages	Document ID	Title
115	19880628		US 4753750 A	Liquid laundry detergent composition and method of use
116	19880628		US 4753748 A	Nonaqueous liquid automatic dishwashing detergent composition with improved rinse properties and method of use
117	19880607		US 4749512 A	Liquid laundry detergent composition
118	19870428		US 4661280 A	Built liquid laundry detergent composition containing salt of higher fatty acid stabilizer and method of use
119	19870407		US 4655954 A	Low phosphate or phosphate free nonaqueous liquid nonionic laundry detergent composition and method of use
120	19870310		US 4648983 A	Built non aqueous liquid nonionic laundry detergent composition containing urea stabilizer and method of use
121	19861111		US 4622173 A	Non-aqueous liquid laundry detergents containing three surfactants including a polycarboxylic acid ester of a non-ionic

	Issue Date	Pages	Document ID	Title
122	19840619		US 4455249 A	Stabilized bleach and laundering composition
123	19840522		US 4450089 A	Stabilized bleaching and laundering composition
124	19840417		US 4443352 A	Silicate-free bleaching and laundering composition
125	19840207		US 4430244 A	Silicate-free bleaching and laundering composition
126	19831206		US 4419482 A	Products containing polymer chains, the preparation and use thereof

	Issue Date	Pages	Document ID	Title
127	19821207		US 4362837 A	Process for preparing products containing polymer chains having ionic links and their use
128	19790522		US 4155637 A	Developing apparatus for developing diazotype material according to the semi-dry process

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3	L3	25300	l1 same l2
4	L4	0	"protein z-dependent protease inhibitor$2"
5	L5	42	"ZPI"
6	L6	5	l3 same l5
7	L7	22374	l3 and (inhibit$3 or prevent$3)
8	L8	297	"protein Z"
9	L9	9594	l3 same (inhibit$3 or prevent$3)
10	L10	16	l9 same l8
11	L12	5	l10 and l11
12	L11	128	Broze.in.

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